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Ovulation induction and cancer risk

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Objective: To review and critique the literature regarding ovulation induction and cancer risk.
Design: Identification of relevant clinical and epidemiological literature through PubMed and other sources.
Conclusion(s): Ovulation and associated hormonal changes have been linked with selected cancers, raising concerns regarding ovulation-inducing agents. Clinical studies have suggested potential links, but more definitive analytic investigations have been difficult to interpret given the small numbers, short follow-up, and imprecise information on drugs or indications for usage. Prospective studies have been limited by inabilities to control for other cancer predictors (including parity), while selective recall has been a concern for retrospective studies. Reports of large increases in ovarian cancer risk associated with fertility medications have not been replicated by more recent investigations. Some findings, based on small numbers, suggest slight increases in risk associated with fertility drugs among nulligravid women or after extended follow-up or for certain tumor subtypes, but further replication is needed. Fewer studies have assessed relationships with other hormonally related cancers, but limited findings support the need for further monitoring of long-term effects for breast and endometrial cancers. Findings regarding other cancers are extremely limited but should be pursued for cancers showing evidence of hormonal influences, including colon cancers and melanomas. (Fertil Steril® 2005;83:261–74. ©2005 by American Society for Reproductive Medicine.)

Key Words: Ovulation induction, fertility drugs, infertility, cancer, risk, epidemiology

Ovulation-inducing drugs are among the fastest growing group of drugs, with prescriptions in the United States nearly doubling between 1973 and 1991 (1). Further increases in rates of use can be expected, given recent projections that by the year 2025 between 5.4 and 7.7 million women aged 15–44 will be diagnosed with some form of infertility (2).

A number of investigations have attempted to address the long-term effects of ovulation-inducing drugs on cancer risk, but most have had shortcomings. These include small numbers of study subjects, short follow-up times, imprecise information on drug exposures and the indications for usage, and absence of information on other correlates of drug exposure that could influence cancer risk. In this review, we discuss a number of relevant studies, focusing on the methodologies employed, their findings, and future directions to clarify fully the effects of the various regimens used for the treatment of infertility.

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BACKGROUND

Three lines of evidence raise concern regarding potential effects of ovulation-inducing drugs on cancer risk. First, the most commonly used medications, clomiphene citrate and gonadotropins, are effective for stimulating ovulation, a factor implicated in the etiology of both breast and ovarian cancers (3, 4). Second, these drugs raise both E_2 and P levels (5), hormones that are recognized as affecting the development and growth of breast and gynecologic cancers as well as some other cancers. Finally, as elaborated below, some clinical and epidemiological studies have linked use of these drugs with an increased incidence of various cancers.

APPROACHES USED IN PREVIOUS STUDIES

Some clinical studies have suggested a link between ovulation-inducing medications and the risk of various cancers, but the absence of comparison groups in such studies precludes definitive conclusions. Analytic studies that provide more definitive results have relied on both retrospective and prospective approaches to evaluate relationships of medication use to subsequent cancers.

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To identify all previous studies undertaken on the effects of fertility drugs on cancer risk, we conducted PubMed searches, using combinations of specific key words and MeSH terms. We gathered information on all English-language publications on the topic undertaken since fertility medications were first marketed in the early 1960s. Epidemiological studies were carefully reviewed with respect to methodological strengths and weaknesses. Information regarding ongoing studies was sought through conversations with a variety of investigators known to be involved with active research. This provided some additional information about preliminary results of investigations, often published as abstracts for presentations made at large national and international meetings.

Given that there have been no clinical trials of the effects on cancer risk of ovulation-inducing agents, the next best evidence derives from prospective or cohort studies (reviewed in Table 1). Such studies are preferable to some other designs because they define exposures before the onset of disease. Most cohort studies, however, have been limited by the small numbers of observed cancers and by a lack of information on other predictors of cancer risk. Many cohort studies have had short follow-up periods, and thus effects that require long latency intervals may remain undetectable. Participants in these studies are often still young and have not yet reached the age of peak cancer incidence.

The availability of appropriate comparison groups is also problematic for cohort studies. In many of these studies, the disease experience of cohorts of infertile women is compared with the experience of the general population through the calculation of standardized incidence ratios (SIRs). SIRs compare the number of observed cancers in the cohort of interest to the number expected based on incidence rates in the general population. The general population incidence rates take into account age, race, and calendar time but have no information about the likely differences in other cancer predictors between infertile women and the rest of the population. Of notable concern is the inability to adjust for parity, a recognized risk factor for breast, endometrial, and ovarian cancers (6–8). Additionally, anovulation, a major indication for drug usage, has been linked in a number of studies with increased risks of endometrial (9–12) and possibly breast (9, 13–19) cancers. Other causes of infertility have also been related to the risks of subsequent cancers: endometriosis to ovarian (20–24) and breast (22, 23) cancers and tubal factor to ovarian cancers (24–27). Thus, comparisons of cancer rates among infertile women (with or without ovulation induction) with cancer rates in the general population can be difficult to interpret.

Cohort studies are most informative if they allow internal comparisons that enable adjustment for a variety of potential cancer risk factors. The calculation of relative risks (RRs) rather than SIRs enables comparison of disease risks between treated and untreated women, while holding constant (or controlling for) other predictors of cancer risk. Few cohort studies, however, have had access to data on other risk factors. Only two of the cohort studies have attempted collection of information directly from study subjects (28, 29). One other study collected information from medical records on ovarian cancer cases and on a limited sample of nondiseased subjects, extrapolating to the entire population through a case-cohort approach (30).

Case-control studies have also been used to assess drug relationships. This study design allows a focus on large numbers of selected cancer cases but must rely on retrospective assessment of drug information, usually through recall by the patients. Because recall of treatment information may differ between cancer-affected and -nonaffected women, there is a potential for reporting bias. Information on the indications for drug use also is likely to be quite imprecise. Since these studies usually focus on an unselected sample of cases diagnosed in the general population (rather than on, for example, a group of infertile women), the use of fertility medications is generally low. Thus, even though case-control studies may start with a large number of subjects, their ability to evaluate specific associations with fertility drugs may be limited. For example, in a recently published population-based study of breast cancer (31), which included 4,566 cases and 4,676 controls, less than 5% of the study subjects reported prior fertility drug use. The resulting analyses involved drug exposure among only 184 cases and 200 controls.

Results from case-control studies can be influenced by the choice of a control group. For example, some studies have selected controls from women who are hospitalized. Since hospitalized women are likely to have better access to and more use of medical services compared with controls selected from the general population, studies using hospital controls may derive different risk estimates than those employing controls selected from the general population.

Prospective studies are not always superior to retrospective studies because both types of studies are subject to various biases. Losses to follow-up are common in prospective studies. Although poor rates of response to questionnaires are a particular concern for case-control studies, they are also problematic for cohort studies if information on potential confounding variables is attempted through questionnaires. Surveillance bias can also come into play in both retrospective as well as prospective studies: women who receive fertility drugs are under close medical scrutiny and therefore likely to have tests that detect certain cancers.

When interpreting reported disease associations, one must give particular consideration to the strengths and limitations of the individual studies. A review of findings by cancer site is provided below.

OVARIAN CANCER

Numerous clinical reports have expressed concern about a potential link between the use of ovulation-inducing drugs

TABLE 1

Review of major cohorts reporting associations between fertility drugs and cancer risk.

Location	No. of subjects	Years evaluated	Average years of follow-up	Measure of association	Covariate information[a]	No. of observed cancers					
						Ovarian	Breast	Endometrial	Melanoma	Cervical	Thyroid
Israel (18)	2,575	1964–74	12.3	SIR	a, b, c, n	4	15	5	4	0	4
United States (30, 69, 82, 87)	3,837	1974–85	12.3	SIR, RR	a, b, f–h, j, l–n	11			12	36	
Australia (64)	10,358	1978–92	6.5	SIR, RR	a, b, e, m, n	6	34	5	16	6	
Israel (Tel Hashomer) (12)	2,496	1964–74	21.4	SIR	a, b, e	12	59	21	8	3	8
Israel (Beer-Sheba) (17)	1,197	1960–84	17.9	SIR	a, b, e, n	2	20	2		4	3
Australia (19)	29,666	before 1994	8.5	SIR	a, b, e, m, n	13	143	12			
United States (45)	51,371	1965–98	5.6	SIR, RR	a–c, f–i, n, s	50					
The Netherlands (29)	25,152	1980–95	5.6	SIR, RR	a–b, f–h, j, m–o, p–r	17	116	14	34		
United Kingdom (46)	5,556	1975–89	7.9	SIR, RR	a, b, f	6	55	4		3	
Israel (Tel Aviv) (15)	5,026	1981–92	3.6	SIR	a, b, e	1	11	2	3	1	1
Israel (Tel Aviv) (63)	1,082	1984–92	6.5	SIR	a, b, e	3	5		2	3	
United States (28)	12,193	1965–88	18.8	SIR, RR	a–d, f–s	45	292	39			

Note: RR = relative risk; SIR = standardized incidence ratio.

[a]Covariates: a = age; b = calendar time; c = race or ethnicity; d = study site; e = residence or country of origin; f = gravidity or parity; g = age at first birth; h = age at menarche; i = family history of cancer; j = oral or other types of contraceptives; k = hormone therapy; l = weight or body mass; m = cause of infertility; n = previous fertility drug use; o = breast or gynecologic operations; p = smoking; q = alcohol; r = physical activity; s = education; t = interviewer.

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and ovarian cancer risk (32–39). The association has biologic credibility, given that "incessant ovulation" and associated alterations in endogenous hormones during the reproductive years are plausible explanations for several factors that alter disease risk, including nulliparity and oral contraceptive use (3, 40). Concerns regarding the effects of fertility medications intensified after publication of two epidemiological studies implicating usage with marked elevations in the risk of ovarian cancer.

Whittemore and others conducted a meta-analysis of 12 case-control studies of the etiology of ovarian cancer. Only three of these, with 526 cases and 966 controls, provided information regarding the use of fertility drugs, and there was scant information about the type of drug or the extent of its use (27). Self-reported prior use of fertility medications was associated with an odds ratio (OR) of 2.8 [95% confidence interval (CI), 1.3–6.1] as compared with women who had no history of infertility. The OR is the measure of risk that can be calculated from case-control studies.

This risk was essentially limited to the subgroup of nulligravid women, who experienced a 27-fold increase in risk associated with fertility drug use (95% CI, 2.3–315.6). This risk estimate approximates the risk of lung cancer associated with extensive smoking and was widely reported in the press. The report caused great concern among physicians who had been prescribing these drugs and patients who received them. Editorials and literature reviews soon appeared to dispute the conclusion of a markedly increased risk (41–44), pointing out that the risk estimate was based on only 12 exposed cases and one exposed control. Moreover, fertility drug use among gravid women was associated with a nonsignificant OR of 1.4.

Rossing and colleagues conducted the other major study that raised concern (30). It was a retrospective cohort study of 3,837 women evaluated for infertility in a single Seattle practice between 1974 and 1985 and followed for cancer incidence through a regional cancer registry. The investigators collected information on drug exposures and indications for use from medical records and attempted to control for effects of other potential confounding variables by abstracting data from medical records of all ovarian cancer cases and from a subcohort sample of 135 women. Using appropriate case-cohort analytic techniques, they estimated that clomiphene use was associated with an adjusted 2.3-fold increased risk (95% CI, 0.5–11.4), based on nine ovarian cancers.

Use of clomiphene for less than 1 year was not associated with an increased risk, but five of the nine women with cancer had taken the drug for 12 or more monthly cycles, resulting in a relative risk of 11.1 (95% CI, 1.5–82.3). An enhanced risk associated with long-term treatment was observed in both those with and without ovulatory abnormalities. A large proportion of the observed tumors were borderline (five of the 11 in the cohort).

Table 2 reviews the Rossing et al. study and other selected cohort investigations that have evaluated ovarian cancer risk in relation to fertility drugs. The Rossing et al. study considered internal comparisons among the members of that cohort; most other studies detailed in Table 2 made comparisons with the general population, while several involved both internal and external comparisons. Several recent cohort studies have failed to provide confirmatory evidence for a large increase in ovarian cancer risk associated with use of fertility drugs. The most recently published of these studies was a multicenter retrospective cohort study conducted in five U.S. areas (28). This study followed 12,193 infertile women for a median of 18.8 years and had detailed information on drug exposures and causes of infertility from medical records as well as questionnaire data on potential cancer risk factors for a substantial proportion of the patients. This study was unique in being able to identify subjects who underwent a bilateral oophorectomy and were thus no longer at risk for developing ovarian cancer. The number of ovarian cancers, 45, was larger than in other cohort studies, but this number was still too limited for analyses of small subgroups of women. The results were largely reassuring, showing no increases in risk associated with ever use of either clomiphene or gonadotropins. There were nonsignificant increases in risk (range of RRs, 1.5–2.5) associated with the use of either clomiphene or gonadotropins among the subjects followed for the longest periods of time, that is, 15 or more years.

One other U.S. study, published to date only in abstract form, also found no evidence for an effect of ovulation-inducing drugs on ovarian cancer risk. After 5.6 years of follow-up of 51,371 patients seen for conception difficulties or ovum donation in 15 California clinics between 1965 and 1998, 50 ovarian cancers were diagnosed (45). The only significant associations with ovarian tumor risk observed in the study were with length of time in infertility treatment and nulligravidity. However, no associations of risk were found for ovulation-inducing drugs and risk, even when dose, formulation, and number of treatment cycles were considered.

While these studies focused primarily on women exposed to ovulation-inducing agents at earlier times, a number of other studies have concentrated on exposures received during IVF. Among 29,666 women referred to 10 Australian IVF clinics, 13 ovarian cancers were observed during a follow-up period averaging 7.8 years (19). The investigators had detailed information on indications for fertility drug use, but only limited information on patient characteristics. The SIR overall was 0.99, with no higher risk for the women who underwent at least one IVF treatment cycle (0.88) as compared with those who received no drug treatment (1.16). Women with unexplained infertility were at a significantly increased risk compared with the general population, but within this subgroup there was no difference in risk between treated and untreated women.

In a cohort of 25,152 women treated for subfertility in The Netherlands, 17 ovarian cancers developed during 5.6 years of follow-up (29). The strengths of this study included de-

TABLE 2

Selected cohort studies reporting associations between fertility drugs and ovarian cancer risk.

Location	Total cohort size [no. of ovarian cancers]	Standardized incidence ratios (95% CIs): comparison with general population		Relative risk (95% CI): comparison of drug use vs. no use within cohort	
United States (30)	3,837 [11]	No drug	1.4 (0.2–5.0)	Clomiphene	2.3 (0.5–11.4)
		Clomiphene	3.1 (1.4–5.9)	≥12 cycles	11.1 (1.5–82.3)
		hMG/FSH	5.6 (0.1–31.0)	hCG	1.0 (0.2–4.3)
		hCG	2.8 (0.6–8.0)		
Israel (Tel Hashomer) (12)	2,496 [12]	No treatment	1.6 (0.6–3.5)		
		All treatments	1.7 (0.6–3.8)		
		Clomiphene	2.7 (0.9–5.8)		
Australia (19)	29,666 [13]	No IVF	1.2 (0.5–2.6)		
		IVF	0.9 (0.4–1.8)		
The Netherlands (29)	23,592 [15]	No IVF	1.4 (0.4–3.2)	IVF	0.4 (0.1–1.2)
		IVF	1.4 (0.7–2.6)		
		≥7 cycles	1.8 (0.0–9.8)		
United Kingdom (46)	5,556 [6]	No treatment	1.7 (0.2–6.0)	Treatment	0.6 (0.1–3.0)
		Treatment	0.8 (0.2–2.2)		
United States (28)	12,193 [45]	No clomiphene	2.1 (1.4–3.0)	Clomiphene	0.8 (0.4–1.5)
		Clomiphene	1.8 (1.0–3.0)	≥15 years of follow-up	1.5 (0.7–3.2)
		No hMG	2.0 (1.4–2.7)	hMG	1.1 (0.4–2.8)
		hMG	2.3 (0.7–5.3)	≥15 years of follow-up	2.5 (0.7–8.3)

Note: Shown are cohort studies with at least five observed ovarian cancer cases.

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tailed information on causes of infertility and drug exposures from medical records as well as on cancer risk predictors obtained through completed questionnaires from many of the study subjects. Thus, the study was able to assess risks associated with different parameters of drug exposures, while adjusting for other risk factors. The results showed no difference in risk between treated and untreated subjects, even when the number of cycles or ampules received were considered.

Reassuring results regarding the effects of fertility drugs on ovarian cancer risk have also emerged from a number of case-control studies (see Table 3), including a meta-analysis of eight studies involving data on 1,060 cases and 1,337 controls (24). In this study, after adjustment for types of infertility, the risk associated with fertility drug use was somewhat higher among nulligravid women (1.8) and among those who had more than 4 months of exposure (RRs, 1.5–1.7), but none of these risks was statistically significant.

These recent studies are in agreement with a number of smaller investigations that found no effect of ovulation-inducing drugs on ovarian cancer risk. These have included cohort (12, 15, 17, 18, 29, 46, 47) (Table 2) as well as case-control (48–51) (Table 3) investigations. The prospective studies have been limited by the small numbers of ovarian cancers, with the number of patients ranging from two in the smallest study (17) to 12 in the largest study (12), and limited information on causes of infertility or on other factors (such as parity, oral contraceptive usage, and socioeconomic status) that could independently influence ovarian cancer risk. The findings from the case-control studies were also limited by the small numbers of ovarian cancer cases reporting prior fertility drug use. For example, in the largest case-control study (51), based on 1,031 cases and 2,411 hospital controls, only 1.1%–1.5% of the subjects reported prior use of fertility drugs, resulting in only 15 cases and 26 controls with relevant exposures for analysis.

While the results of the most recent studies are consistently reassuring when compared with the results of earlier studies, several observations indicate a need for further monitoring. These include the findings in the two most recent studies (24, 28) of modest increases in risk estimates with either extended follow-up or increased exposure to ovulation-inducing drugs. Given that these medications became

TABLE 3

Case-control studies reporting associations between fertility drugs (FDs) and ovarian cancer risk.

Location	No. of cases (% exposed to fertility drugs)	No. of controls (% exposed to fertility drugs)	Type of controls	Comparison	OR (95% CI)	Covariate information[a]
China (26)	229 (2.6)	229 (0.4)	Population	FDs vs. no use	2.1 (0.2–22.7)	f, h, o, s
United States (27)	718 (2.8)	1,236 (0.9)	Hospital and population	FDs vs. no infertility	2.8 (1.3–6.1)	a, d, j
				Nulligravids	27.0 (2.3–316)	
				Gravids	1.4 (0.5–3.6)	
Italy (48)	195 (1.0)	1,339 (1.1)	Hospital	FDs vs. no use	0.7 (0.2–3.3)	a, e, f, j, p, s
Israel (47)	164 (12)	408 (7.1)	Population	FDs vs. no use	1.3 (0.6–278)	a, e, f, i, l, s, t
				Clomiphene	0.9 (0.3–2.3)	
				hMG	3.2 (0.9–11.8)	
Denmark (49)	684 (20.7)	1,721 (23.8)	Population	FDs vs. no use (nulliparous women)	0.8 (0.4–2.0)	a, e, j, k, l
				Clomiphene	0.7 (0.2–2.0)	
				hMG/hCG	0.8 (0.2–3.7)	
Italy (50)	971 (0.5)	2,758 (0.4)	Hospital	FDs vs. no use	1.1 (0.4–3.3)	a, f, i, j, s
				≥6 cycles	1.0 (0.2–3.8)	
Italy (51)	1,031 (1.5)	2,411 (1.1)	Hospital	FDs vs. no use	1.3 (0.7–2.5)	a, f, i, j, s
United States (24)	1,060 (14.1)	1,337 (15.0)	Population	FDs vs. no use (subfertile women)	1.0 (0.8–1.3)	a, c, f, d, j, i, m, s
				Nulligravids	1.8 (0.7–4.2)	
				Gravids	0.7 (0.5–1.0)	

[a]Adjustment factors: a = age; b = calendar time; c = race or ethnicity; d = study site; e = residence or country of origin; f = gravidity or parity; g = age at first birth; h = age at menarche; i = family history of cancer; j = oral or other types of contraceptives; k = hormone therapy; l = weight or body mass; m = cause of infertility; n = previous fertility drug use; o = breast or gynecologic operations; p = smoking; q = alcohol; r = physical activity; s = education; t = interviewer.

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available in the United States beginning in the early 1960s, women who were exposed to them are just beginning to enter the ovarian cancer age range. Thus, additional follow-up data are needed to evaluate their effects.

In addition, both of these recent investigations (24, 28) and Whittemore et al.'s early meta-analysis (27) found drug effects to be greatest among nulligravid women, suggesting the possibility of an enhanced effect of the medications among women with certain indications for use.

The issue of whether fertility drugs might have different effects depending on other patient characteristics has received only minimal attention in most previous studies. Several studies have assessed the relationship between ovarian cancer and fertility drug use according to causes of infertility. When drug effects are observed, it must be questioned whether they are the results of the drug exposure itself or of the reasons for which the drug was prescribed (often referred to as confounding by indication). Although the Rossing et al. study noted increased risks associated with clomiphene use among both women with and without ovulatory abnormalities (30), the multicenter U.S. retrospective cohort study found no evidence of an increase in risk associated with clomiphene use in any subgroup (although the highest risk at 1.0 was indeed found among those with anovulatory problems) (28).

A possible additional subgroup of interest with respect to effects of fertility drugs are women at high genetic risk for ovarian cancer. The one study that evaluated this potential interaction failed to find any unusual effects, although the power to detect an association was quite limited (28).

It has also been questioned whether fertility medications might have a preferential effect on certain ovarian tumor types. Clear cell (52), malignant germ cell (53), and granulosa cell (39) tumors have been linked by case reports to the use of ovulation-inducing drugs. The rarity of these three tumor types makes it difficult to evaluate the reality of the associations through epidemiological investigations. Granulosa cell tumors appear to be of particular interest, given evidence that gonadotropins can induce these tumors in rodents (54) and stimulate cells in human *in vitro* models (55). However, arguing against a specific relationship for granulosa cell tumors are descriptive data from Finland, which show decreases in the incidence of this tumor concomitant with increasing use of ovulation inducers (56).

That ovulation-inducing drugs might preferentially affect the risk of borderline ovarian tumors is suggested by several studies. Both cohort (30, 47) and case-control (24, 57) investigations have shown risk ratios in the range of 3–4 associated with fertility drug use. In one study, the relationship was restricted to nulligravid women (24), and in another, specifically to gonadotropins (47). These findings, in conjunction with case reports of ovarian cancer developing in women during or shortly after treatment with ovulation-inducing agents (32–39), have led to speculations that ovarian stimulation may induce growth in existing highly differentiated indolent tumors. Alternatively, the findings simply could reflect more intensive medical surveillance among infertile women.

Based on the evidence to date, there is no conclusive link between fertility drug use and ovarian cancer. However, most of the studies have had relatively small numbers and/or short follow-up. Additional studies should continue to monitor long-term effects and assess whether there may be distinctive relationships for borderline ovarian tumors and certain tumor histologies. Specific attention should also be focused on effects among women who remain nulligravid.

BREAST CANCER

The epidemiology of breast cancer has been extensively studied, with many investigations supporting the notion of an important etiologic role for endogenous as well as exogenous hormones (6). Surprisingly few studies have addressed the potential relationships to breast cancer risk of use of fertility drugs, despite their recognized effects on ovulation and hormone patterns (4, 58) and clinical reports that have suggested an association (38, 59–62).

For the most part, both cohort (12, 18, 19, 29, 46, 63, 64) (Table 4) and case-control (65–67) (Table 5) studies that have assessed the relationship of fertility medications to breast cancer risk have not found any remarkable associations. Most of these studies, however, were limited by the small numbers of cancers, imprecise information on patterns of or indications for drug use, or incomplete ability to control for other correlates of risk, including well-recognized reproductive risk factors.

Several studies have suggested links of fertility drugs with breast cancer risk, but the results are conflicting, with some suggesting potential increases in risk and others decreases. A recent case-control study involving over 4,500 breast cancer cases was able to carefully control for potential confounding variables but had to rely on self-reports of infertility and had few women exposed to fertility drugs (31). Although this study found no association of risk related to use of clomiphene, there was some indication of a risk elevation among women with long-term use of menopausal gonadotropins. Use for at least 6 or more months or at least six cycles was associated with ORs ranging from 2.7 to 3.8. The finding was somewhat unexpected given that neither of the constituents of hMG—FSH and LH— are thought to have direct effects on breast tissue (68). Since gonadotropin therapy increases both serum estrogen and P levels, the investigators suggested this as a possible explanation for their findings. Whether the increases in hormones that would be associated with six or more cycles of exposure would be sufficient to substantially affect the subsequent risk of breast cancer is questionable (68).

The opposite relationship, namely, a nonsignificantly reduced risk of invasive and *in situ* breast cancer associated

TABLE 4

Selected cohort studies reporting associations between fertility drugs and breast cancer risk.

Location	Total cohort size [no. of breast cancers]	Standardized incidence ratios (95% CIs): comparison with general population		Relative risks (95% CI): comparison of drug use vs. no use within cohort	
United States (69)	3,837 [27]			Clomiphene	0.5 (0.2–1.2)
				≥12 cycles	0.6 (0.2–2.4)
				hCG	0.5 (0.2–1.8)
Israel (Tel Hashomer) (12)	2,496 [59]	No treatment	1.4 (1.0–2.0)		
		All treatments	1.1 (0.7–1.6)		
		Clomiphene	1.2 (0.7–1.9)		
		Clomiphene + hMG	1.6 (0.7–3.4)		
Australia (19)	29,666 [143]	No IVF	0.9 (0.7–1.2)		
		IVF	0.9 (0.7–1.1)		
The Netherlands (29)	23,592 [95]	No IVF	1.0 (0.7–1.4)	IVF	1.0 (0.6–1.5)
		IVF	1.1 (0.8–1.4)		
		≥7 cycles	0.8 (0.2–2.1)		
United Kingdom (46)	5,556 [55]	No treatment	1.2 (0.6–2.0)	Treatment	1.0 (0.5–1.9)
		Treatment	1.2 (0.8–1.6)		
United States (72)	12,193 [292]	No clomiphene:	1.3 (1.1–1.5)	Clomiphene	1.0 (0.8–1.3)
		Clomiphene:	1.3 (1.1–1.6)	≥20 years of follow-up	1.4 (0.9–2.1)
		No hMG:	1.3 (1.1–1.4)	hMG	1.1 (0.7–1.6)
		hMG:	1.4 (0.9–2.0)	≥20 years of follow-up	1.5 (0.8–3.2)

Note: Shown are cohort studies with at least 25 observed breast cancer cases.

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with clomiphene (adjusted RR = 0.5; 95% CI, 0.2–1.2) was found in Rossing et al.'s retrospective cohort study (69). This estimate was based on only 12 exposed cases, and there was no indication of any further risk reduction with extended duration of use. A chemopreventive effect of clomiphene would be of interest given that it is a selective estrogen receptor modulator (SERM) and thus could have properties similar to another SERM, tamoxifen (70). Additional epidemiological support of a reduced risk of breast cancer associated with clomiphene use was provided in a recently published abstract from the Nurses Health Study II (71), which showed a RR of 0.40 (95% CI, 0.2–0.7) associated with use of clomiphene among women treated for ovulatory infertility. The risk decreased significantly with duration of use of clomiphene, with users of 10 or more months having an RR of 0.21 relative to nonexposed women. The findings were based on self-reports of both drug use as well as causes of infertility.

On the other hand, the recent multicenter U.S. cohort study failed to find either a decreased risk associated with clomiphene or an increased risk associated with gonadotropins (72). With 292 breast cancer cases occurring during follow-up, the study had considerable power to evaluate these relationships. Ever use of clomiphene or gonadotropins was unrelated to risk. However, there were small nonsignificant increases in risk after extended follow-up periods (≥20 years), with the RRs in the range of 1.4–1.6, similar to the long-term risks observed for ovarian cancer in this same cohort study. When analyses were restricted to invasive breast cancers, the RR after 20 years of follow-up for clomiphene use became statistically significant (RR = 1.6; 95% CI, 1.0–2.5).

Other epidemiological investigations that had sufficient power to assess relationships with breast cancer according to detailed parameters of fertility drug use are the Australian (19) and Dutch (29) follow-up studies of IVF patients. Both studies failed to find an overall difference in risk between exposed and unexposed subjects. However, in the Australian study, an approximately twofold increased risk of breast cancer was observed within 1 year of last treatment. This prompted the suggestion that ovulation-inducing drugs might promote the rapid growth of preexisting tumors, similar to the short-term transient increase in breast cancer after a recent pregnancy (73). However, several other studies that

TABLE 5

Case-control studies reporting associations between fertility drugs (FDs) and breast cancer risk.

Location	No. of cases (% exposed to fertility drugs)	No. of controls (% exposed to fertility drugs)	Type of controls	Comparison	OR (95% CI)	Covariate information[a]
Italy (65)	2,569 (3.3)	2,588 (2.9)	Hospital	Fertility treatment vs. none	1.1 (0.8–1.5)	a, d, f–j, o, s
				FD use vs. no use	1.4	
United States (67)	2,173 (8.5)	1,990 (7.4)	Population	Clomiphene or other drug use among those with difficulty conceiving	0.9–1.0	a, c, d, f, g,
				Medications among women with difficulty maintaining a pregnancy	1.0	
Italy (66)	3,415 (0.5)	2,916 (0.4)	Hospital	Ever FD vs. no use	1.2 (0.5–2.6)	a, f
				Nulliparous women	0.6 (0.2–2.3)	
				Parous women	2.2 (0.7–6.6)	
United States USA (31)	4,566 (4.0)	4,676 (4.3)	Population	Ever FDs vs. no use	0.9 (0.8–1.2)	a, c, d
				≥6 cycles clomiphene	1.0 (0.7–1.3)	
				≥6 cycles hMG	2.7 (1.0–6.9)	
				Ever FDs vs. no use among women diagnosed with infertility	1.2 (0.8–1.7)	
				≥6 cycles clomiphene	1.2 (0.7–2.0)	
				≥6 cycles HMG	3.8 (1.2–11.8)	

[a]Adjustment factors: a = age; b = calendar time; c = race or ethnicity; d = study site; e = residence or country of origin; f = gravidity or parity; g = age at first birth; h = age at menarche; i = family history of cancer; j = oral or other types of contraceptives; k = hormone therapy; l = weight or body mass; m = cause of infertility; n = previous fertility drug use; o = breast or gynecologic operations; p = smoking; q = alcohol; r = physical activity; s = education; t = interviewer.

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have assessed detailed timing effects of last drug use found no support for a promotional effect by either clomiphene or gonadotropins (29, 72).

In the Australian study, Venn and others also assessed causes of death among their cohort of infertile women, observing nonsignificant decreases in mortality for most causes as compared with the general population (74). This included deaths due to breast cancer, which showed no appreciable differences between those who did and did not undergo IVF. The data therefore provided little support for another report that demonstrated poor prognostic features among breast cancer patients with recent histories of exposure to fertility drugs (75).

Given that breast cancer is widely recognized as having a hormonal etiology, further assessment of the effects of ovulation-inducing drugs should be undertaken. Studies to date have shown both decreases as well as possible increases in risk. Additional studies that can account for effects of other recognized risk factors (including delays in fertility) should be undertaken.

ENDOMETRIAL CANCER

Endometrial cancers are well recognized as hormonally sensitive (8). There is a clinical report of three cases of adenomatous hyperplasia of the endometrium, a precursor condition, occurring among women exposed to ovulation-inducing agents (76). Few analytic studies, however, have assessed the relationship between endometrial cancer and use of fertility drugs. One small case-control study that assessed the relationship found no association, but, with only seven exposed cases, the investigation had limited power to detect an effect (77). Most cohort studies (see Table 1) have not observed an association, but the majority had follow-up times of less than 10 years and few associated cases of uterine cancer (between 2 and 14; see Table 1) (17, 19, 29, 46, 64).

The two larger cohort studies both raise some concern regarding effects of ovulation-inducing agents on the endometrium. In one of the Israeli cohorts in which 21 uterine cancers were diagnosed during an average of more than 20 years of follow-up, a significant twofold increase in risk was associated with fertility drug use (12). Similarly, the multicenter U.S. cohort study, which detected 39 cases of endometrial cancer among cohort members, found clomiphene use associated with a nonsignificant increase in risk (RR = 1.8; 95% CI, 0.9–3.3) (78). Further, increases in risk were found among subjects with higher dosages of exposure or longer follow-up periods, with trends in risk for the latter variable being statistically significant. Drug effects were also more apparent among nulligravid and obese women (RRs of 3.5 and 6.0, respectively).

Because tamoxifen, a SERM that bears structural similarities to clomiphene (5), has been repeatedly linked with increases in endometrial cancer risk (79), these two studies raise concern despite the fact that they were based on fairly small numbers of cancers.

Few studies have been undertaken to assess the relationship between ovulation induction and endometrial cancer. Based on the two largest studies that demonstrate somewhat increased risks (similar to what has been previously observed for another SERM, tamoxifen), further study of the relationships appears warranted.

MELANOMA

The potential role for hormones in the etiology of melanomas has received increasing attention (80), and this raises the question of possible effects of fertility medications. Although several clinical reports suggest a relationship (35, 81), few epidemiological studies have addressed the question.

The largest study assessing the effects of fertility drugs on the risk of melanoma has been the Dutch IVF follow-up study (29). A total of 34 melanomas were observed during follow-up, but there was no difference in risk between the exposed and unexposed patients. The other three cohort investigations that assessed the effects of fertility drugs on the occurrence of melanoma have had limited numbers of women who developed melanomas. These include the Rossing et al. study in Seattle (12 cases) (82) and two investigations in Australia (12 and 14 cases, respectively) (64, 83). In the Seattle study (82), no overall association was found with drug use, but nonsignificant increases in melanoma risk were associated with 12 or more cycles of clomiphene (RR = 2.2; 95% CI, 0.5–10.2) and hCG (1.7, 0.5–6.2). However, it was unclear whether these increases were due to effects of the drugs or to some underlying hormonal abnormalities among the women. The Australian study of Venn and others (64) found no overall risk associated with drug usage but could not evaluate effects of specific fertility drugs. The other Australian study (83), which focused on 3,186 women attending an infertility clinic, 14 of whom developed melanoma, is difficult to interpret. All cases were exposed to fertility medications, but women who developed melanoma had fewer cycles of exposure to fertility medications than other cohort members. Patients with male factor infertility were at increased risk of developing melanoma compared with the general population, which, given universal drug exposure, was interpreted as indicative of an adverse effect of fertility medications among women with normal hormonal milieus.

In one case-control study, no unusual risk associated with use of fertility drugs was observed (84). However, numbers of infertile women reporting prior histories of ovulation-inducing drug usage were presumably small.

The available evidence does not allow any conclusions regarding this association. Further study may be warranted.

OTHER CANCERS

Data regarding the relationship of ovulation-inducing drugs to the risk of other cancers are sparse, but limited data exist with respect to cervical, thyroid, and trophoblastic tumors.

Although cervical cancer is not generally viewed as a hormonally related tumor, purported relationships of the disease with parity (85) and use of oral contraceptives (86) have raised concerns regarding the effects of other hormonal agents. The most informative data derive from the Seattle study (87) in which 36 *in situ* and invasive cervical cancers were detected. In line with other studies, which have shown that parity is a risk factor for this cancer (85), infertile women were at a decreased risk of developing cervical cancer as compared with the general population. The risk among women who had taken clomiphene was reduced relative to nonusers (RR = 0.4; 95% CI, 0.2–0.8), but there was no apparent relation according to duration of use. The investigations recommended further assessment of the hypothesis that use of antiestrogenic agents leads to a reduced risk of cervical neoplasia.

Thyroid cancer is another site of interest with respect to hormonal factors, primarily because of its predominance among females. In a pooled analysis of 13 case-control studies from North America, Asia, and Europe, use of fertility drugs was found to be associated with a 60% increase in thyroid cancer risk (95% CI, 0.9–2.9) (88). One of the studies included in this meta-analysis also individually reported a significant four-fold excess risk associated with use of fertility drugs (89). It was not possible in either this study or the meta-analysis to determine if the treatment itself or other correlates of infertility were responsible for the observed risk.

Given that ovulation-inducing drugs cause ovulation of more than one oocyte, it has been questioned whether the increase in the production of immature or anucleated oocytes might increase the risk of developing gestational trophoblastic tumors, particularly persistent ones. Several instances of gestational trophoblastic tumors, oftentimes occurring with a coexisting fetus, have been found among women exposed to ovulation-inducing agents (90–93). Cohort studies have been difficult to undertake given the rarity of the condition. Hydatidiform moles were reported to occur at a rate of 1/659 among 2,369 clomiphene-induced pregnancies, a rate considerably higher than the natural incidence of 0.5–1.1/1,000 (93). A recent comprehensive review of the literature concluded that women having a singleton pregnancy after exposure to ovulation inducers had no additional risk of persistent trophoblastic tumors compared with those who conceive without drugs (94). Since ovulation-inducing agents often lead to multiple pregnancies, which is a recognized risk factor for persistent trophoblastic tumors, patients treated with these drugs are at an increased risk relative to those conceiving without them.

Colon cancer has been suggested as possibly having a hormonal etiology, largely because of observations of inverse associations of risk with parity and use of hormone therapy (95). This raises some interest in the possible effects of fertility medications. To our knowledge, this issue has been examined in only one prior investigation, which found no relationship to fertility drugs, although it was based on extremely small numbers (only one case occurring among IVF exposed women vs. three among unexposed women) (64).

Scant data on this topic prohibits any conclusions. The rarity of some of these cancers will make further assessment difficult.

FUTURE RESEARCH NEEDS

Given that clomiphene was first approved for clinical use in 1967 and gonadotropins in 1969, the women who first used these drugs during their late 20s and early 30s have only recently reached the age when hormonally related cancers are common. Most studies cited in this review are reassuring in not showing a strong association between use of these medications and risks of most cancers. On the other hand, several studies have found increasing risks with greater exposures or extended follow-up, indicating that complacency is not warranted and that long-term effects should be further monitored, especially in view of the changes in reproductive technology. There has been little attention focused on the long-term effects of assisted reproductive technologies, which often involve much higher exposures to gonadotropins than were received by women in previous eras. In addition, most IVF protocols include luteal phase support for several weeks with supplemental progestogens, which raises concern since these agents have been linked to increases in breast cancer risk (96). Since *in vitro* techniques have become common only in the last couple of decades, it may be some time before epidemiological studies can amass the follow-up times required to fully address long-term effects.

There is some consistency across studies showing a modest enhancement of ovarian cancer risk associated with use of fertility drugs among women who remain nulligravid (24, 27, 28). This may indicate an interactive effect of the drugs with the underlying causes of infertility, including those reflecting unique hormonal perturbations. On the other hand, it may be that women who continue to remain infertile may have received larger doses of longer durations of fertility drugs than other women.

There are other issues of interest that have not been widely pursued. First is the question of whether women at particularly high risk of cancer, including those with a genetic predisposition, experience unusual risks from the use of fertility medications. Second, it is of interest whether fertility drugs have unusual effects among women who have used other hormones. This includes oral contraceptives, which have been shown to be associated with reduced risks of endometrial and ovarian cancers (97) and somewhat in-

creased risks of breast cancers (98), and menopausal hormone therapy, which has been linked with increases in the risk of all three cancer sites (8, 96, 99).

Some (24, 30, 47, 57), although not all (28), studies suggest an unusual occurrence of borderline ovarian cancers among women exposed to fertility medications. Whether this reflects a biologic effect or is merely the result of more intensive surveillance of women treated with these drugs by ultrasound and clinical examination warrants further scrutiny. Biologically, it is of interest that estrogen receptor expression is a common feature of borderline ovarian tumors. Thus, further study of the relationship of fertility medications to ovarian as well as breast cancers according to hormone receptor status would appear warranted. In addition, investigations of cancer associations by tumor histologies should also be undertaken, given clinical reports of several unusual types of ovarian cancer (e.g., granulosa cell tumors) occurring among fertility drug users.

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